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BOOK OF ABSTRACTS

September 5 – 8, 2010 · Bologna/Italy

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30th International Symposium on the Separation of Proteins, Peptides and Polynucleotides

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3rd International Symposium on Biothermodynamics

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LMP_C_26.03

Comparing Approaches for Drug-Like Molecules Solubility Calculations

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Solubility has been recognized as one of the most important properties for designing separation and purification processes of complex molecules, such as active pharmaceutical ingredients. Experimental solubility data are usually needed for performing such design operations. However, frequently data are unavailable due to reduced amounts of sample, time limitations, or inherent complexities with experimental measurements. In such cases, thermodynamic models can be the more theoretically sound tools to generate solubility estimates.

In this work, the group-contribution method UNIFAC, and the NRTL-SAC activity coefficient model, are used to correlate and predict solubility in pure and mixed solvents of a set of representative drug-like molecules such as benzoic, salicylic and acetylsalicylic acids, ibuprofen, hydroquinone, estriol, estradiol and resveratrol. Generally, UNIFAC and NRTL-SAC models are able to represent the data, with NRTL-SAC being better for pure solvent solubilities. Solubility dependence with temperature and solvent composition were also taken into account.

Whenever possible, the reference solvent approach was also applied, and the results were generally improved with any of the models. The average percent absolute deviations obtained for the representation of solubility data in pure solvents are very satisfactory, but for mixed solvents higher deviations are possible to find.

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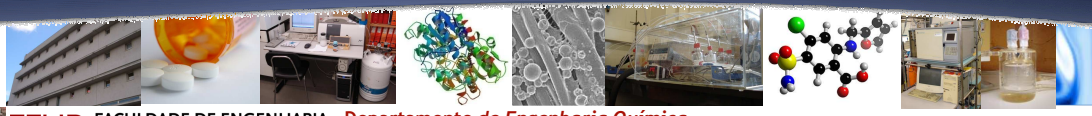

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Introduction

- **Solubility:** one of the most important properties for designing separation and purification processes of complex molecules, such as active pharmaceutical ingredients;
- Solubility data are frequently unavailable. So, even if experimental data are still fundamental, predictive thermodynamic tools must be implemented;
- Solubilities of benzoic, salicylic and acetylsalicylic acids, ibuprofen, hydroquinone, estriol, estradiol and resveratrol were studied in a variety of pure and mixed solvents using several models.

NRTL-SAC model[1]

- It characterizes the effective surface interactions between solute and solvent in terms of predefined conceptual segments.
- A small set of experimental data are used to identify molecular parameters for the solutes, and the model is used to extrapolate to other systems and conditions.

Group-contribution methods[2,3]

- Besides to UNIFAC, the A-UNIFAC model is applied. It takes into account association effects; an association activity coefficient term is added to the original equation which is a function of the fraction of non-bonded sites.

Modelling

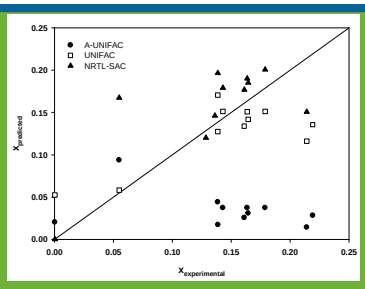
Results

RSA [4]

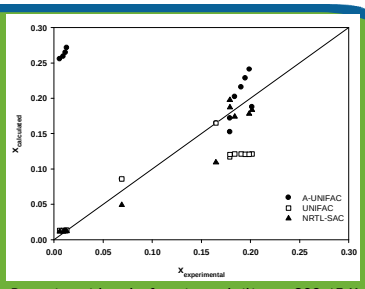
- The Reference Solvent Approach is an alternative, that avoids the knowledge of the solute melting properties minimizing the impact of uncertainties.
- It involves the selection of a reference solvent, relative to which all solubility calculations are made.

AAD's for solubility prediction in pure solvents at 298.15 K.

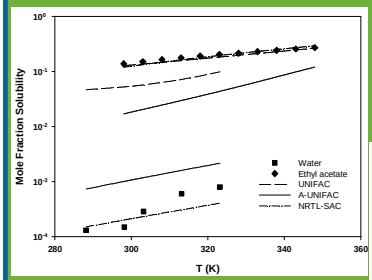
Compound	A-UNIFAC	A-UNIFAC + RSA	UNIFAC	UNIFAC + RSA	NRTL-SAC	NRTL-SAC + RSA
Salicylic acid	75.1	38.7	18.9	18.9	18.4	13.7
Benzoic acid	24.0	19.1	29.7	29.7	27.9	14.0
Acetylsalicylic acid	72.3	29.6	78.3	30.2	36.9	37.0
Ibuprofen	44.8	47.3	36.7	40.9	71.0	57.2
Estriol	>150	65.9	28.9	----	>150	----
Estradiol	84.8	----	64.8	33.8	65.0	82.7
Hydroquinone	91.1	----	40.5	----	35.3	----
	65.4	40.1	42.5	30.7	42.4	40.9



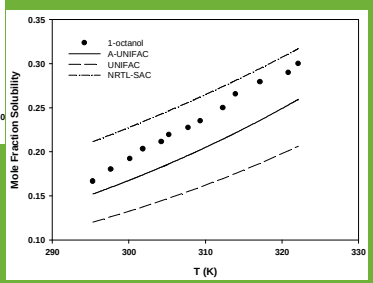
Salicylic acid mole fraction soluility at 298.15 K.



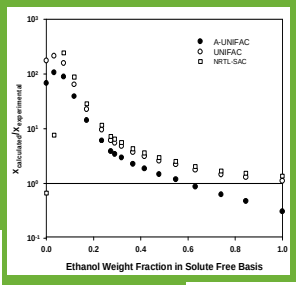
Benzoic acid mole fraction soluility at 298.15 K.



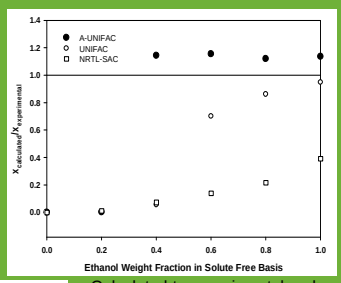
Solubilities of salicylic acid as a function of temperature.



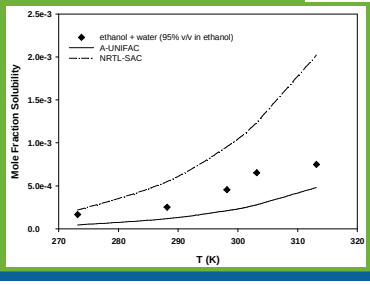
Solubilities benzoic acid as a function of temperature.



Calculated to experimental mole fraction solubilities ratio in ethanol-water for salicylic acid at 298.15K.



Calculated to experimental mole fraction solubilities ratio in ethanol-water for ibuprofen at 298.15K.



Estradiol mole fraction solubility in ethanol-water mixed solvent.

Conclusions

- Generally, UNIFAC and NRTL-SAC models are able to represent the data in pure solvents. To apply the A-UNIFAC more effectively some work is still needed to estimate representative parameters.
- For the solubility dependence with temperature, NRTL-SAC model is slightly better. For aqueous systems, A-UNIFAC is better than UNIFAC proving the need of taking into account association.
- In general, these models fail in the estimation of these compounds solubilities in alcohol/water mixed solvents. However, A-UNIFAC showed better performances.
- Whenever RSA was applied, the results were generally improved with any of the models, excepting some mixed solvent systems where limitations were found.

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